REMARKS

A check for $225 for the requisite fee for a two-month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 74-76, 92-94, 123, 124, 127-133 and 135-139 are pending. Claims 70, 72, 73 and 77-79 are cancelled herein without prejudice or disclaimer. Applicant expressly reserves the right to file a continuation application to the cancelled subject matter. Claims 74, 127 and 135 are amended herein. Claim 74 is amended to more distinctly claim the subject matter by replacing the recitation "about 3-10 nucleotides" with "3-10 nucleotides." Claim 74 also is amended to replace the recitation "about 4-20 nucleotides" with "4-20 nucleotides."

Claim 127 is amended herein to more distinctly claim the subject matter. The recitation "a nucleic acid base is selected and occupies" is replaced with the recitation "a selected nucleotide base occupies" for clarity. Claim 127 also is amended to include the modifier "nucleotide" before the term "base" or "bases" throughout the claim to improve clarity, because the nucleic acid of the probes includes sequences of nucleotides (see, e.g., see page 12, lines 1-6). Claim 127 also is amended to more distinctly claim the subject matter by reciting that the "selected nucleotide base" is adenosine-5'-phosphate, deoxyadenosine-5'-phosphate, deoxythymidine-5'-phosphate, uridine-5'-phosphate, guanine-5'-phosphate, deoxyguanosine-5'-phosphate, cytidine-5'-phosphate or deoxycytidine-5'-phosphate. Basis for the amendment is found throughout the specification (e.g., see page 12, lines 1-6 and page 10, lines 12-27). For example, the specification teaches at page 12, lines 1-6:

> The probes are divided into four subsets. In each, one of the four bases is used at a defined number of positions and all other bases except that one on the remaining positions. Probes from the first subset contain two elements, A and non-A (A=adenosine).

It is known to one of skill in the art that the "four bases" in a ribonucleic acid (RNA) molecule include the ribonucleotides adenosine-5'-phosphate, uridine-5'-phosphate, cytidine-5'-phosphate and guanine-5'-phosphate and that the "four bases" found in a deoxyribonucleic acid (DNA) molecule include the deoxynucleotides deoxyadenosine-5'-phosphate, deoxythymidine-5'-phosphate, deoxyguanosine-5'-phosphate and deoxycytidine-5'-phosphate (e.g., see Zubay, Biochemistry, page 662 (1983), a copy of which is supplied herewith). The element "for each subset, one of the four bases is selected and occupies a defined number of

positions in each probe and all other bases except the selected base occupy the remaining positions" was previously presented and examined in claim 127 (e.g., see the Office Action, mailed November 3, 2004) and deemed free of the prior art of record. Claim 127 was rejected in the November 3, 2004 Office Action under 35 U.S.C. §112, second paragraph because the recitation "the four nucleic acid bases" was allegedly indefinite, because it was deemed "unclear which four (of the at least five) bases are being described." The amendment of claim 127 herein addresses this issue. Claim 135 is amended for clarity. No new matter is added.

REJECTION OF CLAIMS 70, 72, 73 AND 77-79 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 70, 72, 73 and 77-79 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the patent applicant had possession of the claimed subject matter at the time of filing of the application.

In order to expedite prosecution, but without acquiescing to the rejection, claims 70, 72, 73 and 77-79 are cancelled herein without prejudice or disclaimer. Thus, the rejection as applied to these claims is moot.

THE REJECTION OF CLAIMS 70, 72, 74, 76-79, 92-94, 124 AND 136 UNDER 35 U.S.C. §102(e)

Claims 70, 72, 74, 76-79, 92-94, 124 and 136 are rejected under 35 U.S.C. §102(e) as anticipated by Deugau *et al.* (U.S. Patent No. 5,508,169) because Deugau *et al.* allegedly discloses an array of nucleic acid probes having a double-stranded portion and a single-stranded portion. The Examiner alleges that probes of Deugau *et al.* have a terminal nucleotide and the number of nucleotides between the terminus and the double-stranded region varies, and thus concludes that the variable sequence would be between the terminus and the double stranded portion.

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the

invention". *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Claim 74 is directed to an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 nucleotides in length; a longer single-stranded second nucleic acid of about 20-30 nucleotides in length that includes a nucleotide sequence complementary to the first nucleic acid and a random terminal nucleotide sequence of between 3-10 nucleotides in length; and an oligonucleotide of 4-20 nucleotides in length that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single-stranded portion that includes a random terminal nucleotide sequence of between 3-10 nucleotides in length; and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid. Claims 75, 76, 92-94, 123, 124 and 136 depend from claim 74 and are directed to various embodiments thereof.

Disclosure of Deugau *et al.*

Deugau *et al.* discloses indexing linkers that have single-stranded portions on both ends or on only one end. The reference discloses that the double-stranded portion can be at either the 3'-terminus or at the 5'-terminus. Deugau *et al.* discloses that the indexing linkers have a protruding single strand of a unique sequence of 3, 4, or 5 nucleotides, and that neither single-stranded end functions as a restriction endonuclease recognition site. Deugau *et al.* discloses that its single-stranded overhangs are produced by restriction endonucleases, which produce overhangs on each end of a fragment (col. 7, lines 48-60).

Differences between the claimed subject matter and the disclosure of Deugau *et al.*

1. As Directed to Claims 70, 72, 73 and 77-79

In order to expedite prosecution, but without acquiescing to the rejection, claims 70, 72, 73 and 77-79 are cancelled herein without prejudice or disclaimer. Thus, the rejection as applied to these claims is moot.

2. As Directed to Claims 74-76, 92-94, 123, 124 and 136

Applicant respectfully submits that claim 74 is directed to an array of probes each of which includes a first sequence of about 15-25 nucleotides and a second, longer sequence of about 20-30 nucleotides that includes a random terminal nucleotide sequence of between 3-10 nucleotides in length, and an oligonucleotide of between 4 to 20 nucleotides, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double stranded portion and a single stranded portion that includes a random terminal nucleotide sequence of between 3-10 nucleotides in length and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid. When the random terminal nucleotide sequence is ligated to the oligonucleotide, the resulting single-stranded sequence of the probe includes at least 7 nucleotides (3 nucleotides from the random terminal nucleotide sequence and 4 from the ligated oligonucleotide) and up to 30 nucleotides (10 nucleotides from the random terminal nucleotide sequence and 20 nucleotides from the ligated oligonucleotide) that includes a random sequence.

Deugau *et al.* does not disclose an array of nucleic acid probes, where each probe includes a double-stranded portion and a single-stranded portion where the single-stranded region includes a random sequence of 3-10 nucleotides in length ligated to an oligonucleotide of between 4 to 20 nucleotides. As discussed above, Deugau *et al.* discloses that its indexing linkers are terminated by overhangs produced by cleavage with restriction endonucleases and are of a length of 3, 4, or 5 nucleotides, not 7-30 nucleotides as required by the instant claims. Hence, Deugau *et al.* does not disclose every element of the claim 74. Thus, because Deugau *et al.* does not disclose every element of claim 74, Deugau *et al.* does not anticipate claims 74-76, 92-94, 123, 124 and 136.

THE REJECTION OF CLAIMS 127-133 AND 135-139 UNDER 35 U.S.C. §102(b)

Claims 127-133 and 135-139 are rejected under 35 U.S.C. §102(b) as anticipated by Hornes *et al.* (WO 90/06045, published 14 June 1990) because Hornes *et al.* allegedly discloses every element of the claimed array. The Examiner alleges that the non-hybridized target of Hornes *et al.* is a "variable region," the oligo-dT is a "double-stranded portion," that a biotinylated nucleotide at the end or an incorporated ddNTP is a "selected nucleic acid base that occupies a defined number of positions" and "non-biotinylated A, T, C and G" are "all other bases" that occupy the remaining positions, and that page 15 discloses dividing the arrays into for subsets. This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

Claim 127 is directed to an array of nucleic acid probes, where each probe includes a single-stranded portion at one terminus, a double-stranded portion at the opposite terminus, and a variable nucleotide sequence within the single-stranded portion. The probes are divided into four subsets, and for each subset, a selected nucleotide base occupies a defined number of positions in each probe and all other nucleotide bases except the selected nucleotide base occupy the remaining positions. The selected nucleotide base is selected from among adenosine-5'-phosphate, deoxyadenosine-5'-phosphate, deoxythymidine-5'-phosphate, uridine-5'-phosphate, guanine-5'-phosphate, deoxyguanosine-5'-phosphate, cytidine-5'-phosphate and deoxycytidine-5'-phosphate. Claims 128-133, 135, 137 and 138 depend from claim 127 and are directed to various embodiments thereof.

Disclosure of Hornes *et al.*

Hornes *et al.* discloses magnetic particles that have a plurality of oligonucleotide probes that are either directly attached to the magnetic particle or attached via a double-stranded piece of DNA (page 2, lines 9-22). The probes include an oligo-dT sequence and optionally restriction enzyme sites (page 2, lines 25-31). In one embodiment, a DNA molecule having a sequence complementary to a known sequence of a target nucleic acid molecule is hybridized to the probe (having an oligo-dT sequence) via a poly-dA tail on the DNA sequence, and a different labeled "probe" is hybridized to a different sequence of the nucleic acid molecule, forming a ternary complex (page 13, lines 1-11). Hornes *et al.* discloses standard Sanger sequencing reactions (page 14, lines 2-36). Hornes *et al.* discloses a method of sequencing single-stranded nucleic acids that includes dividing particles that include single-stranded DNA or RNA oligonucleotide to be sequenced into four aliquots and adding to each aliquot a polymerase, mixed nucleotide triphosphates and a different dideoxynucleoside triphosphate for each aliquot (page 15, lines 15-37).

Differences between the claimed subject matter and the disclosure of Hornes *et al.*

Hornes *et al.* does not disclose an array of probes where a selected nucleotide base occupies a defined number of positions in each probe and all other nucleotide bases except the selected nucleotide base occupy the remaining positions. Hornes *et al.* discloses incorporating a biotinylated base at the end of the probe as a coupling agent, or incorporating a terminal dideoxynucleoside in the probe to produce a series of labeled DNA strands having different chain lengths and ending with a particular dideoxy base. The Examiner alleges that the

terminal biotinylated base or dideoxynucleoside is the same as the "selected base" occupying a defined number of positions as instantly claimed and that "all other bases" include non-biotinylated A, T, C, and G. The claims, amended for clarity, recite that the "selected nucleotide base" is selected from among adenosine-5'-phosphate, deoxyadenosine-5'-phosphate, deoxythymidine-5'-phosphate, uridine-5'-phosphate, guanine-5'-phosphate, deoxyguanosine-5'-phosphate, cytidine-5'-phosphate and deoxycytidine-5'-phosphate. Thus, the "selected nucleotide base" of the instant claims does not encompass a biotinylated nucleotide nor a dideoxynucleoside.

Hornes *et al.* does not disclose probes where adenosine-5'-phosphate occupies a defined number of positions in each probe and all other nucleotide bases except adenosine-5'-phosphate occupy the remaining positions. Hornes *et al.* does not disclose probes where deoxyadenosine-5'-phosphate occupies a defined number of positions in each probe and all other nucleotide bases except deoxy-adenosine-5'-phosphate occupy the remaining positions. Hornes *et al.* does not disclose probes where deoxythymidine-5'-phosphate occupies a defined number of positions in each probe and all other nucleotide bases except deoxythymidine-5'-phosphate occupy the remaining positions. Hornes *et al.* does not disclose probes where uridine-5'-phosphate occupies a defined number of positions in each probe and all other nucleotide bases except uridine-5'-phosphate occupy the remaining positions. Hornes *et al.* does not disclose probes where guanine-5'-phosphate occupies a defined number of positions in each probe and all other nucleotide bases except guanine-5'-phosphate occupy the remaining positions. Hornes *et al.* does not disclose probes where deoxyguanosine-5'-phosphate occupies a defined number of positions in each probe and all other nucleotide bases except deoxyguanosine-5'-phosphate occupy the remaining positions. Hornes *et al.* does not disclose probes where cytidine-5'-phosphate occupies a defined number of positions in each probe and all other nucleotide bases except cytidine-5'-phosphate occupy the remaining positions. Hornes *et al.* does not disclose probes where deoxycytidine-5'-phosphate occupies a defined number of positions in each probe and all other nucleotide bases except deoxycytidine-5'-phosphate occupy the remaining positions.

In addition, Hornes *et al.* does not disclose an array of probes that includes a single-stranded portion at one terminus, a double-stranded portion at the opposite terminus, and a variable nucleotide sequence within the single-stranded portion, where the array is divided into four subsets. Page 15, lines 15-37 of Hornes *et al.* discloses a method of sequencing single-stranded nucleic acids that includes dividing its paramagnetic particles that include single-

stranded DNA or RNA oligonucleotide attached thereto to be sequenced into four aliquots and adding to each a polymerase, mixed nucleotide triphosphates and a different dideoxynucleoside triphosphate for each aliquot. The probes disclosed on page 15 of Hornes *et al.* are single-stranded. Hornes *et al.* does not disclose dividing an array of probes that include a single-stranded portion at one terminus, a double-stranded portion at the opposite terminus, and a variable nucleotide sequence within the single-stranded portion into four subsets. Hence, Hornes *et al.* does not disclose every element of claim 127. Therefore, because Hornes *et al.* does not disclose every element of claim 127, Hornes *et al.* does not anticipate claims 127-133 and 135-139.

REJECTION OF CLAIMS 73 AND 123 UNDER 35 U.S.C. §103(a)

Claims 73 and 123 are rejected under 35 U.S.C. §103(a) as being unpatentable over Deugau *et al.* in view of Brenner *et al.* (*Proc. Natl. Acad. Sci. USA*, 1989, 86:8902-8906) because Deugau *et al.* allegedly teaches every element of the claimed subject matter except the specific means by which the probes are immobilized, but Brenner *et al.* allegedly cures this defect. The Examiner alleges that Brenner *et al.* teaches that biotin/streptavidin provides a versatile means of capture immobilization. This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would suggest to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.* 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

THE CLAIMS

Claim 123 depends from claim 74. Claim 123 is directed to an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 nucleotides in length; a longer single-stranded second nucleic acid of about 20-30 nucleotides in length that includes a nucleotide sequence complementary to the first nucleic acid and a random terminal nucleotide sequence of between 3-10 nucleotides in length; and an oligonucleotide of 4-20 nucleotides in length that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single stranded portion that includes a random terminal nucleotide sequence of between 3-10 nucleotides in length; and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid. The probes are fixed to a solid support by conjugating to a coupling agent selected from the group consisting of antibody/antigen, biotin/streptavidin, *Staphylococcus aureus* protein A/IgG antibody F_c fragment, nucleic acid/nucleic acid binding protein, and streptavidin/protein A chimeras.

Teachings of the Cited References

Deugau *et al.*

See related section above.

Brenner *et al.*

Brenner *et al.* teaches a fluorescent DNA sequence fingerprinting procedure that couples band separation with sampled nucleotide sequencing (page 8902, col. 2, lines 11-14). The reference teaches cleaving DNA using endonuclease followed by electrophoresis and analysis by fluorescent emissions (paragraph bridging pages 8902-8903). Brenner *et al.* teaches that following specific cleavage using any restriction enzyme, biotin can be attached to each primary cleavage end by adding biotinylated nucleotides (page 8904, col. 1, second full paragraph).

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Deugau *et al.* with the teachings of Brenner *et al.* does not result in the instantly claimed arrays.

Claim 73

In order to expedite prosecution, but without acquiescing to the rejection, claim 73 is cancelled herein without prejudice or disclaimer. Thus, the rejection as applied to claim 73 is moot.

Claim 123

As discussed above in the traverse of the §102(e) rejection, Deugau *et al.* does not teach or suggest an array of probes where each probe includes a single-stranded first nucleic acid of about 15-25 nucleotides in length; a longer single-stranded second nucleic acid of about 20-30 nucleotides in length that includes a nucleotide sequence complementary to the first nucleic acid and a random terminal nucleotide sequence of between 3-10 nucleotides in length; and an oligonucleotide of 4-20 nucleotides in length that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single stranded portion that includes a random terminal nucleotide sequence of between 3-10 nucleotides in length; and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid. Deugau *et al.* does not teach or suggest an array of probes fixed to a solid support by conjugating to a coupling agent selected from the group consisting of antibody/antigen, biotin/streptavidin, *Staphylococcus aureus* protein A/IgG antibody F_c fragment, nucleic acid/nucleic acid binding protein, and streptavidin/protein A chimeras.

Brenner *et al.* does not cure these defects. Brenner *et al.* teaches a DNA fingerprinting technique that includes primary cleavage of the DNA using restriction enzymes or other methods of specific cleavage, attaching biotin to both ends, performing a secondary cleavage, attaching the biotinylated ends to beads, labeling the ambiguous overhangs with fluorescent nucleotide-specific terminators, and eluting the labeled strands for electrophoresis (see page 8904, paragraph bridging the left and right columns and Figure 4). Brenner *et al.* teaches single-stranded ambiguous overhangs of 1, 2 and 4 nucleotides in length (see Fig 1., page 8903). Brenner *et al.* does not teach or suggest a probe having a double-stranded region and a terminal single-stranded region where the single-stranded region includes a random sequence of 3-10 nucleotides in length ligated to an oligonucleotide of between 4 to 20 nucleotides. Hence, even if, arguendo, Brenner *et al.* teaches coupling oligonucleotides to a solid support using biotin, the combination of the teachings of Deugau *et al.* and Brenner *et al.* does not teach or suggest every element of claim 123.

Neither Deugau *et al.* nor Brenner *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe includes a single-stranded first nucleic acid of about 15-25 nucleotides in length; a longer single-stranded second nucleic acid of about 20-30 nucleotides in length that includes a nucleotide sequence complementary to the first nucleic acid and a random terminal nucleotide sequence of between 3-10 nucleotides in

length; and an oligonucleotide of 4-20 nucleotides in length that includes a random nucleotide sequence, where the first nucleic acid is hybridized to the second nucleic acid to form a hybrid having a double-stranded portion and a single stranded portion that includes a random terminal nucleotide sequence of between 3-10 nucleotides in length; and the oligonucleotide is ligated to the random nucleotide sequence of the second nucleic acid, where the probes are fixed to a solid support by conjugating to a coupling agent selected from the group consisting of antibody/antigen, biotin/streptavidin, *Staphylococcus aureus* protein A/IgG antibody Fc fragment, nucleic acid/nucleic acid binding protein, and streptavidin/protein A chimeras. Thus, the combination of teachings of Deugau *et al.* and Brenner *et al.* does not result in the instantly claimed array of claim 123. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

REJECTION OF CLAIM 75 UNDER 35 U.S.C. §103(a)

Claim 75 is rejected under 35 U.S.C. §103(a) as being unpatentable over Deugau *et al.* in view of Ghosh *et al.* (*Nuc. Acids Research* 15: 5353-5372 (1987)) because Deugau *et al.* allegedly teaches every element of the claimed subject matter except conjugation of the probe to the support through a coupling agent, or the specific material from which the support is made, but Ghosh *et al.* allegedly cures this defect. This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

Claim 75

Claim 75 depends from claim 74 and is directed to an embodiment where the array of claim 24 is fixed to a solid support selected from the group consisting of plastics, ceramics, metals, resins, gels, membranes, and chips.

Teachings of the Cited References

Deugau *et al.*

See related section above.

Ghosh *et al.*

Ghosh *et al.* teaches the direct covalent attachment of DNA to solid supports having alkyl-amino and alkyl-carboxylic functionalities. Ghosh *et al.* teaches covalently attaching oligonucleotides having a length of 17-29 bases to a solid support (page 5353 and page 5363) Ghosh *et al.* teaches a number of chemical methods for the attachment of DNA to solid

supports through stable covalent linkages, including carbodiimide-mediated end attachment or phosphodiester bonds (page 5354). Ghosh *et al.* teaches polystyrene, plastics and resins as solid supports (see pages 5356-5357).

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Deugau *et al.* with the teachings of Ghosh *et al.* does not result in the instantly claimed arrays.

As discussed above, Deugau *et al.* does not teach or suggest an array of probes where each probe has a double-stranded region and a single-stranded region, where the single-stranded region includes a random sequence of 3-10 nucleotides in length ligated to an oligonucleotide of between 4 to 20 nucleotides.

Ghosh *et al.* does not cure this defect. Ghosh *et al.* provides limited information on the oligonucleotides used, teaching their length (page 5353 and page 5363) and methods of derivatizing the oligonucleotides (page 5358). Ghosh *et al.* does not teach or suggest an array of nucleic probes, nor a probe that includes a double-stranded region and a single-stranded region, where the single-stranded region includes a random sequence of 3-10 nucleotides in length ligated to an oligonucleotide of between 4 to 20 nucleotides. Hence, even if, arguendo, Ghosh *et al.* teaches covalent coupling of oligonucleotides to a solid support, or plastics and resins as a solid support, combining the teachings of Deugau *et al.* and Ghosh *et al.* does not teach or suggest every element of claim 75.

Neither Deugau *et al.* nor Ghosh *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe has a double-stranded region and a single-stranded region, where the single-stranded region includes a random sequence of 3-10 nucleotides in length ligated to an oligonucleotide of between 4 to 20 nucleotides. Thus, the combination of teachings of Deugau *et al.* and Ghosh *et al.* does not result in the instantly claimed arrays of claim 75. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner fails to set forth a *prima facie* case of obviousness.

* * *

In view of the amendments and remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

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18

STRUCTURE OF NUCLEIC ACIDS AND NUCLEOPROTEINS

Nucleic acids are long-chain polymers composed of nucleotides. The sequence of nucleotides is the repository of all genetic information carried by chromosomes. Despite this, not all nucleic acid is informational, nor is all the informational nucleic acid found in the chromosome. Examples of non-informational nucleic acid include ribosomal RNA and centromeric DNA, whose functions are primarily structural. Examples of informational nucleic acids not found in chromosomes include nucleic acids of mitochondria, chloroplasts, plasmids, and viruses. Most of the chapters in Part IV and Chapters 27 and 28 in Part V are devoted to explaining the ways in which nucleic acids are replicated and transmit their genetic information for use in the cell. In this chapter the focus is on the basic structural properties of nucleic acids in the free-solution state and as they exist in protein complexes in cells.

Electron micrograph of a human chromosome in late-prophase. (Magnification 21,000×.) The chromosome consists of two identical chromatids united at their centromeres. The chromatin consists primarily of a complex of DNA and histone (see text). It is still a mystery as to what forces cause the condensation of the nucleohistone into this highly condensed form. (Micrograph obtained from Gunter F. Bahr, M.D.)

NUCLEOTIDES, THE BUILDING BLOCKS OF NUCLEIC ACIDS

There are two chemically different types of nucleic acids, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Both DNA and RNA contain four different nucleotides. Each *nucleotide* contains a nitrogenous base known as a *purine* or a *pyrimidine*; a sugar, *ribose* in RNA; *deoxyribose* in DNA; and a phosphoryl group. The nucleotide may be converted to a *nucleoside* by removal of the phosphate. The primary structure of the four commonly occurring deoxyribonucleotides found in DNA are shown in Figure 18-1.

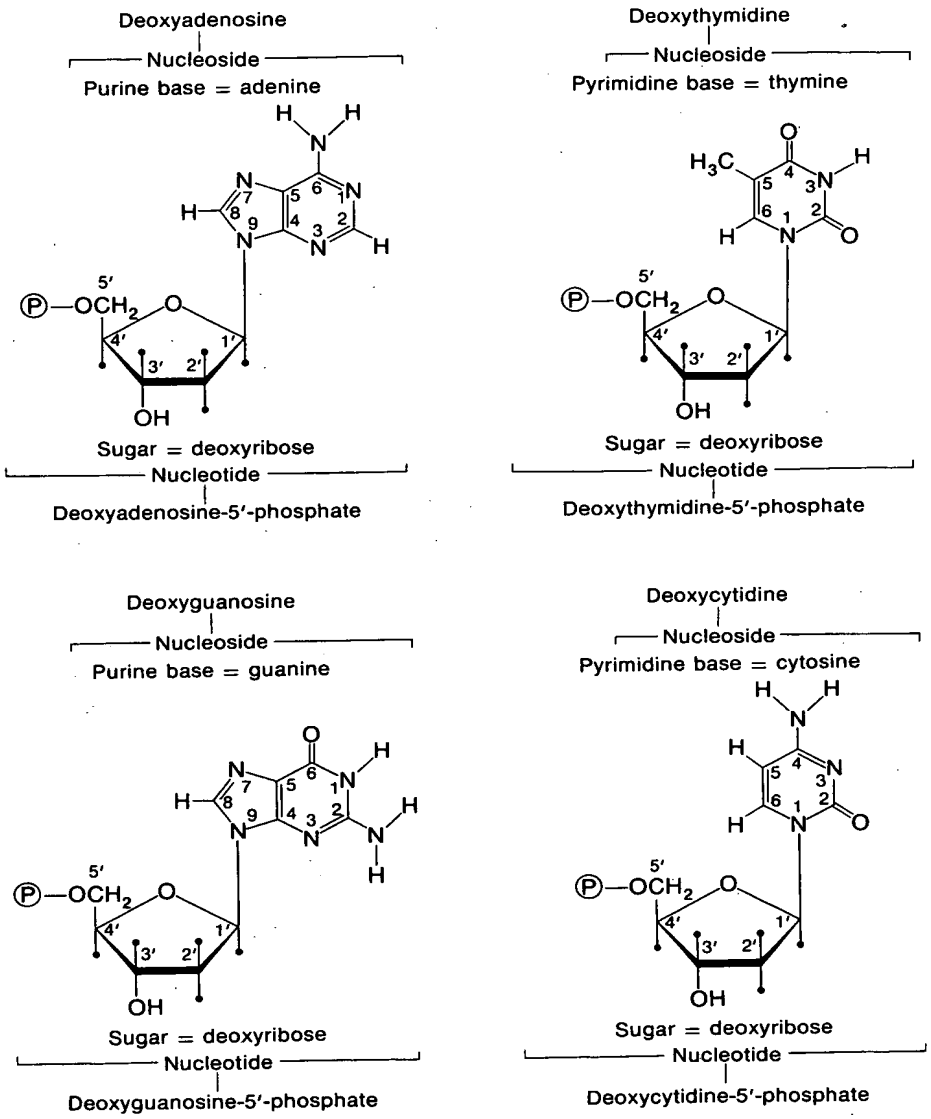

Figure 18-1
Structure of four deoxyribonucleotides found in DNA. Note the numbering system for the carbon and nitrogen atoms of the purine and pyrimidine bases. The carbon atoms of the sugars are usually given prime designations. Note that the nitrogen bases are cis relative to the C-5′ and trans relative to the C-3′-OH.

Table 18-1
Ionization Constants of the Ribonucleotides (Presented as p*K* Values)

	Base	Secondary Phosphate	Primary Phosphate
Adenosine-5′-phosphate (5′-AMP)*	3.8	6.1	0.9
Uridine-5′-phosphate (5′-UMP)	9.5	6.4	1.0
Cytidine-5′-phosphate (5′-CMP)	4.5	6.3	0.8
Guanine-5′-phosphate (5′-GMP)	2.4, 9.4	6.1	0.7

*5′-AMP (or 5′-rAMP) refers to the ribonucleotide. The comparable deoxyribonucleotide (deoxynucleotide) is indicated by the symbol 5′-dAMP.

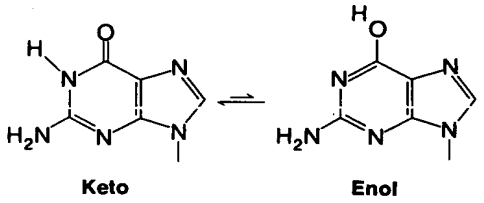

Figure 18-2
Keto-enol isomerization of guanine.

Compositional variability in the nucleotide is accounted for solely by the purine or pyrimidine base attached to the C-1′ position of the sugar (atoms in the sugar are commonly given a prime designation). These bases are either the purines, *adenine* and *guanine*, or the pyrimidines, *thymine* and *cytosine*. The same bases are found in RNA, except that thymine is replaced by *uracil*, which has an H— group instead of a CH_3— group on the C-5 position of the pyrimidine. The sugar in ribonucleotides is also different in having an additional HO group on the C-2′ which is cis with respect to the C-3′-OH.

All the commonly occurring nucleosides and nucleotides are capable of existing in two tautomeric forms. For example, guanosine (G) can undergo the keto-enol shift shown in Figure 18-2. The keto form is strongly favored, so much so that it is difficult to detect even trace amounts of the enol form. Similarly, the keto forms of thymidine (T) or uridine (U) are strongly preferred. Adenosine (A) and cytidine (C) can isomerize to imino forms (not shown), but once again the amino forms (shown) are strongly preferred. Even though the unusual tautomers are present in very small amounts, it is conceivable that they are contributors to the mutation process.

Some nucleotides undergo protonation in acid and some undergo deprotonation in base; the relevant p*K*s are indicated in Table 18-1. At neutrality there is no charge on any of the bases. Three of the bases undergo protonation as the pH is lowered (A, C, and G). X-ray diffraction and spectroscopic analysis (nuclear magnetic resonance and infrared spectroscopy) have been used to show that adenosine protonates on the N-1 position of the purine rather than on the amino group (see Figure 18-3). The charged form is stabilized by the resonance hybrids shown. On cytidylic

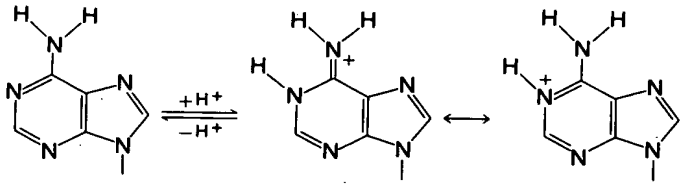

Figure 18-3
Uncharged and protonated forms of adenosine. The charged base resonates between the two structures shown on the right.